(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number : **0 473 431 A1**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number : **91307913.3**

(22) Date of filing : **29.08.91**

(51) Int. Cl.[5] : **A61K 9/50,** A61K 9/52, A61K 9/20

(30) Priority : **30.08.90 US 575465**

(43) Date of publication of application : **04.03.92 Bulletin 92/10**

(84) Designated Contracting States : **DE ES GB IT**

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(54) **Rotogranulations and taste masking coatings for preparation of chewable pharmaceutical tablets.**

(57) Chewable medicament tablets are made from coated rotogranules of a medicament wherein the rotogranules are formed from a granulation mixture of medicament, e.g. famotidine binder, e.g. polyvinylpyrrolidone, and carrier, e.g. lactose and the rotogranules are coated with cellulose acetate, cellulose acetate butyrate or a combination thereof and polyvinyl pyrrolidone and a process for making such tablets and a method of providing taste masking of medicaments utilizing such coated rotogranules.

EP 0 473 431 A1

Field of the Invention

This invention relates to tablets containing means to mask the taste of active ingredients. More particularly, the taste masking of active ingredients is achieved by rotogranulating active material with a binder and carrier material and coating such rotogranulations with a taste masking polymer coating.

BACKGROUND OF THE INVENTION

Orally administered medicaments are given to the patient in many forms, such as liquid solutions, emulsions, or suspensions, or in solid form such as capsules or tablets (as used herein, the term "tablet" means any shaped and compressed solid dosage form, including caplets). Medicaments administered in tablet or capsule form are usually intended to be swallowed whole. Therefore, the often disagreeable taste of the active ingredient need not be taken into account in formulating the medicine, except for the provision of means to prevent the taste from being apparent during the short time that the medicine is in the mouth. Such means may include the provision of an appropriately thin and quickly dissolving coating on the tablet, the use of the gelatin capsule form (the gelatin outer shell of the capsule keeps the active ingredient inside until the capsule has been swallowed), or simply compressing a tablet firmly so that it will not begin to disintegrate during the short time that it is intended to be in the mouth.

Children, older persons, and many other persons have trouble swallowing whole tablets and even capsules. Therefore, in cases where the dosage to be administered cannot be made into a very small tablet or capsule, it is desirable to provide the medicine either in liquid form or in a chewable solid form, in addition to the tablet or capsule that is designed to be swallowed whole. Even where the medicine can be formulated as a liquid, it is desirable also to be able to provide a chewable solid form (i.e. tablets) because of added convenience versus carrying a supply of liquid medicine.

A common problem with chewable tablet forms is the often disagreeable taste of the active ingredient which manifests itself during chewing. In some cases, the taste of the active medicament in a tablet can be overpowered by adding flavoring ingredients to the tablet so that when it is chewed, the taste of the active ingredient is simply overpowered. For instance, this has been done with children's aspirin where the dosage is small enough so that the amount of flavoring agents needed to mask the taste of the medicine is not so great that the tablet becomes unreasonably large. A different approach is taken with a commercially available children's size tablet of acetaminophen (acetyl para-aminophenol or "APAP") wherein the APAP is present in granules that are coated with ethyl cellulose. A significant proportion of the APAP remains shielded by the coating (and therefore does not contribute to taste) while the tablet is in the mouth, despite some breakage of the ethyl cellulose coating during compression of the tablet and some additional breakage of the coating during chewing. The APAP becomes bioavailable via permeation through the coating (although ethyl cellulose is not soluble in aqueous fluids, water does permeate through the coating) and from the granules where the coating is broken.

U.S. Patent No. 4,851,226, issued July 25, 1989, discloses chewable medicament tablets wherein granules of active ingredient are directly coated with a blend of cellulose acetate or cellulose acetate butyrate and polyvinylpyrrolidone. While such direct coating of pharmaceutical active with this polymer blend may be acceptable for certain applications, e.g. taste masking of active particles which are smooth and of uniform size, it has been found to be unacceptable as applied to active compositions whose raw granules are small and irregularly shaped such as famotidine because of poor dissolution and taste masking results.

EP-A-O 411 952 discloses chewable medicament compositions comprising a rotogranulation blend of from about 88 to about 97.5% medicament, about 2 to about 10% polyvinylpyrrolidone (PVP) and about 0.5 to about 2.0% sodium lauryl sulfate (SLS), by weight of the weight of the total composition. In further embodiments a coating of hydroxyethyl cellulose (HEC) or a mixture of hydroxyethyl cellulose and hydroxypropyl methylcellulose (HPMC) is added to these rotogranulated particles. The HEC and HEC/HPMC coatings provide excellent taste masking while still permitting acceptable bioavailability of the active ingredient including poorly water soluble (at low pH) ibuprofen.

EP-A-91304631.4 discloses a chewable medicament comprising a coating for active medicament comprising a polymer blend of cellulose acetate and/or cellulose butyrate and water soluble hydroxypropyl cellulose to provide a taste masked and/or sustained release coating. The rotogranulations and/or coating methods disclosed in EP-A-O 411 952 and EP-A-91304631.4 are not applicable to small and irregularly shaped granules of active compositions like famotidine because of difficulty in providing smooth even coats on the particles for good taste masking and dissolution of the medicament.

The present invention is directed to the discovery of a granulating and coating process for active medicaments which can achieve a better balance between taste masking, dissolution and rate of bioavailability when applied to irregularly shaped raw granules of compositions like famotidine than other previously known coating

combinations.

SUMMARY OF THE INVENTION

As embodied and fully described herein, the present invention provides a medicament comprising a rotogranulation composition comprising about 4 to 10% of a binder material, about 10 to 94% of a carrier material and about 2 to 85% of an active material by weight of the total rotogranulation and a coating for such rotogranulation comprising a polymer coating comprising a blend of one or both of cellulose acetate (CA) or cellulose acetate butyrate (CAB) and polyvinylpyrrolidone (PVP), preferably, in a ratio of CA and/or CAB:PVP of from about 95:5 to 60:40 preferably about 80:20 of CA:PVP. In preferred embodiments of the invention, the coated rotogranulated medicament is included in a chewable tablet.

In further preferred embodiments, the coated medicament comprises: a medicament selected from the group consisting of famotidine, loperamide, cimetidine and ranitidine, more preferably famotidine of a particle size in the range of about 5 to 75 microns. The medicament is rotogranulated with a binder, preferably selected from the group consisting of PVP, starch or hydroxypropyl methyl cellulose, more preferably PVP with a particle size range of 50 to 150 microns; a carrier composition such as fine particle size lactose, fructose, mannitol, sucrose, dextrose, maltodextrins, confectioner's sugar or mixtures thereof, more preferably lactose with a particle size of between 5 to 75 microns to produce a granulation which is substantially spherical in shape. The rotogranulated medicament is coated with about 10% by weight of the total weight of the coated particles with CA and/or CAB: PVP, preferably about an 80:20 blend of CA:PVP. The polymer coating preferably comprises about 5 to 20% by weight of the total weight of the coated rotogranulated medicament composition. The coated particles are then compressed into tablet form together with excipients and flavoring agents to produce chewable tablets.

The invention also provides a process of making the rotogranulated particles and methods of using the rotogranulated particles to make chewable tablets.

Brief Description of the Drawings

Fig. 1 is a reproduction of a microphotograph of irregularly shaped raw famotidine granules showing a scale of 200 μm.

Fig. 2 is a reproduction of a microphotograph of famotidine granules rotogranulated with lactose and polyvinylpyrrolidone in accordance with the invention showing a scale of 500 μm.

Fig. 3 is a reproduction of a microphotograph of a cellulose acetate/polyvinylpyrrolidone coated rotogranule in accordance with the invention showing a scale of 200 μm.

DETAILED DESCRIPTION OF THE INVENTION

The invention will now be described specifically in terms of its most preferred embodiments which are the preparation of rotogranulations of famotidine and chewable tablets comprising coated rotogranules of famotidine. Famotidine is a histamine H_2-receptor antagonist useful for inhibiting gastric secretion and treating ulcers. Uncoated famotidine has an unpleasant or bitter taste absent its proper barrier separation or masking from the mouth. Reference will also be made in detail herein to other preferred embodiments of the compositions, processes and methods of the invention.

In accordance with preferred embodiments of the invention granules of medicament, preferably raw famotidine, PVP and lactose are rotogranulated with water to produce nearly spherical granulated particles. These rotogranulated particles are preferably in the size range of about 150 to 400 microns.

The rotogranulation is preferably formed by blending about 2 to 85% by weight raw famotidine with about 4 to 10% by weight PVP and about 10 to 94% by weight of lactose. Percentages by weight are by weight of the total rotogranulation composition.

Details of a preferred process of rotogranulating and subsequent fluid-bed coating are provided in the examples section. Preferred methods are further described in: Jones, D. M. "Factors to Consider in Fluid-Bed Processing," Pharmaceutical Technology, April 1985, Pg. 50-63; and Jager, K. F. et al., "Effect of Material Motion on Agglomeration in the Rotary Fluidized-Bed Granulator", Drugs Made in Germany, Vol. XXV, Pg. 61-65 (1982). The entire disclosure of these articles are hereby incorporated herein by reference. Granulations comprising famotidine, PVP and lactose produced by rotogranulation in accordance with the invention are nearly spherical in shape and will be referred to hereinafter as "rotogranules".

Rotogranules have increased strength due to the compaction or densification of the granulation mixture as rotogranules are formed by rotation in the rotogranulator bed. The famotidine rotogranules have excellent

integrity and enough strength to withstand fluid bed coating processes without significant breakage. This resistance to breakage is advantageous since broken particles are of a smaller size and are not readily coated in subsequent coating steps. Smaller sized particles without proper coating detract from the taste masking purpose of the coating by providing poor taste to the mixture as a whole. Further, smaller sized particles tend to agglomerate and interfere with subsequent fluid bed coating operations.

Irregularly shaped raw famotidine granules are illustrated in Fig. 1. The irregular and small particle size of these raw granules are undesirable for direct coating because such small particles may escape coating and/or the irregularly shaped particles require a higher amount of coating to completely cover the entire surface of the granule. Such high and uneven amounts of coating results in poor dissolution and taste mask properties. It has been found in accordance with the present invention that rotogranulation of raw famotidine with lactose and PVP produce spherical particles, see Fig. 2, which are readily coated to provide good taste mask and dissolution properties thereto. Fig. 3 illustrates a coated rotogranule in accordance with the invention.

PVP or povidone acts as a binder in the granulation process. Use of PVP as a binder imparts good mechanical strength to the granules. In this respect PVP is superior to other binders such as cellulosic polymers, but other such polymers may be used, e.g. hydroxypropyl methylcellulose or starch.

Lactose is a carrier which adds bulk and smoothness to the body of the granules and may increase the release rate and dissolution of the only slightly water soluble famotidine. Other useful carrier materials which may be substituted for lactose include other saccharides, e.g. fructose, sucrose, dextrose, confectioner's sugar and maltodextrins. The carrier materials should be of fine particle size, preferably in the range of 5 to 75 microns to fill in surface voids and provide a smooth surface to the rotogranule.

Further, microcrystalline cellulose may be blended into such carrier materials and incorporated into the rotogranules. Fine particle size microcrystalline cellulose may be added to such carrier materials in the range of about 5-20% of such materials to provide increased strength to the rotogranules.

In preferred embodiments of the compositions and processes of the invention, medicament, preferably famotidine in rotogranular form, with binder and carrier ingredients, is coated with a blend of CA and/or CAB/PVP polymer. The coated rotogranules, together with other ingredients such as flavoring agents, extenders, excipients, and the like, are compressed into tablet form. (As used herein, the term "rotogranule" refers to individual rotogranulated particles.)

Cellulose acetate and cellulose acetate butyrate are quite water insoluble but are soluble in organic solvents. They can provide good taste masking properties since they do not dissolve in the mouth and are tough enough to remain effectively intact during processing and normal chewing in the mouth. If used alone, however, a coating of CA and/or CAB would not provide adequate bioavailability of the active ingredient after swallowing the chewed tablet. To provide the requisite bioavailability, polyvinylpyrrolidone (PVP) is added to the coating mixture. PVP is a polymer which is soluble in both water and organic solvents. The water solubility of PVP provides bioavailability of the coated active medicament in the gastrointestinal (GI) tract. When the coated granules are swallowed, the active medicament becomes bioavailable via permeation as the coating disintegrates.

Permeation can occur through the intact coating but is encouraged by the disintegration of the coating which becomes porous through dissolution of the water soluble PVP.

The CA and/or CAB:PVP polymer blend also has good mechanical flexibility which is advantageous in a product where the coating must withstand the forces of tablet compression and chewing in the mouth. A high enough proportion of CA and/or CAB and PVP coating remains effectively intact on the famotidine rotogranules through the compression of the tablet and through normal chewing in the mouth to permit effective taste masking of the unpleasant tasting famotidine. The term "effectively intact" means that the coating remains sufficiently integral to mask the taste or flavor of the medicament. This taste masking is effective to mask the unpleasant flavor of the medicament without requiring large and bulky amounts of overpowering flavoring agents.

The solubility of PVP in organic solvents permits ready mixing with CA or CAB during the production of the coated granules, since CA and CAB are not very soluble, if at all, in water, and are more conveniently applied from an organic solvent solution. PVP and CA and/or CAB form clear compatible solutions in organic solvents, preferably acetone/methanol mixtures, which are suitable for pharmaceutical coating. The blend of CA and/or CAB and PVP provides the balance needed for good taste masking while being chewed in the mouth, along with either rapid or sustained bioavailability of the active medicament in the GI tract after swallowing. Generally the ratio of CA and/or CAB to PVP is in the range of about 95:5 to 60:40, preferably the coating is about 80:20; CA:PVP.

The coated granules may be made by coating the rotogranules of medicament with an organic solvent solution of the polymers in a fluidized bed coating operation. A wide variety of organic solvents may be used to prepare the organic solvent solution of the coating polymers. For instance, a preferred solvent is acetone-methanol, but other solvent systems may also be used, including methylene chloride-methanol (e.g. 9:1), acetone-ethyl acetate, toluene-ethanol, and others.

The polymers are dissolved in the solvent and the polymer solution is then coated onto famotidine rotogranules or other medicament active ingredient or combination of ingredients, using a fluidized bed coater. Air (which may be heated) passes through a bed of the medicament granules to fluidize them, and the solvent solution of the two polymers is sprayed onto the fluidized bed and thereby coats the rotogranules. The air passing through the bed dries the coated rotogranules, so that a dry coated granule is obtained. The coated granules are then used in combination with various excipients, flavors, and colors to make a chewable tablet.

The dried coating usually constitutes about 5-20% of the total dry weight of the coated rotogranule. The exact proportions of coating to medicament desired for individual cases can be determined by routine experimentation. The amount of coating may be varied in light of the intended application and desired bulk of the products. Chewable tablets can be acceptable in larger sizes than swallowed tablets since chewing will reduce the size of the tablets in the mouth. Larger proportions of coating may be used to provide a sustained release or better tasting formulation.

When two or more medicaments are utilized in tablets of the present invention the coatings may be varied to provide a slower release of one medicament over another. This is especially advantageous for dosing a combination of medicaments that are more effectively released in different parts of the digestive tract or are better released separately in the digestive tract to avoid interference with each other or other incompatibility. Further, the same medicament may be subject to different coating compositions and amounts to provide for sustained release of some portion of the medicament and immediate release of another portion of the medicament to achieve an optimal dosing versus time profile. Obtaining such optimal dosing/time profiles depends upon the particular medicaments and medical needs required. The exact proportions of coating materials used to achieve these profiles can be determined by routine experimentation.

As a general rule, the proportion of polymer in the solvent solution will be preferably from about 5 to 14, more preferably about 5 to 10 and most preferably about 10 weight percent, depending upon the process parameters. As a practical matter, a concentration of less than 5% CA and/or CAB and PVP polymer blend would unduly lengthen the coating process and a concentration of more than 14% would hamper spraying of the thickened solution.

While exact size of the coated rotogranules has not been found to be critical, the coated granules, are preferably sized in the range of 150 to 400 microns. Particle sizes of less than 150 microns are difficult to coat and particle sizes of greater than 400 microns may provide undesirable grittiness to the finished product. In general, particles of like size facilitate blending and provide regularity to dosage forms.

In addition to famotidine, other solid low bulk, low water soluble medications in need of taste masking can be used in accordance with the the invention. Illustrative additional examples include loperamide, cimetidine and ranitidine their pharmaceutically acceptable salts and combinations thereof and with other medicaments. Identification of medicaments herein is intended to apply to pharmaceutically acceptable salts thereof as well. Further, the coating of the invention provides a convenient means for providing a viable dosage form for combination medicaments which are incompatible before (e.g. during storage) or after administration.

An illustrative preferred procedure for coating the rotogranules of medicament in accordance with the invention is briefly described here and provided in more detail in the following examples section. The medicament, in rotogranular form, is preferably placed in a fluidized bed coater and is fluidized by a flow of warm air. The temperature of the air has not been found to be narrowly critical, and can vary over a wide range, keeping in mind the fact that the temperature should not be high enough to cause decomposition, sintering, or melting of the medicament granules. When coating famotidine rotogranules, a product temperature of from about 35° to 50° C is maintained. The rate of air flow is adjusted so as to fluidize the granules. Such flow will vary depending on factors such as the specific equipment used, the size of the charge of granules, the size of the individual granules, the apparent specific gravity of the granules, and other factors that are known to those skilled in the art of fluidized bed coating.

After the medicament has been fluidized, the polymer solution is sprayed via bottom, top or tangential spray onto the fluidized bed. The air flow through the bed is continued until the amount of solvent remaining in the coating has been greatly reduced. The rotogranules are actually dry to the touch within a very short time after the coating solution has been sprayed onto the granules of medicament; a matter of a few seconds in some cases. The total drying time required to ensure that the solvent content of the coating has been reduced to the level desired may take much longer, depending on the solvent used, temperature of the air, size of the batch, and the like. Routine experimentation will suffice to determine the appropriate air temperatures and total times required in the fluidized bed coaters in individual cases.

The invention will now be illustrated by examples. The examples are not intended to be limiting of the scope of the present invention but read in conjunction with the detailed and general description above, provide further understanding of the present invention and an outline of a process for preparing the rotogranule compositions and chewable medicament tablets of the invention.

EXAMPLES

The Examples below set forth the ingredients and proportions for typical laboratory scale preparations of coated medicament granules. The materials used are the following:

Famotidine - in the form of granules having a particle size of between about 5 to 75 microns;

PVP - in the form of a white powder having a particle size of about 50 to 150 microns.

CA - in the form of a white powder.

Lactose - white to cream colored powder having a particle size of between 5 and 75 microns.

The coating methods used are disclosed for example in Jones, D. M. "Factors to Consider in Fluid-Bed Processing" Pharmaceutical Technology, April 1985 and rotogranulating methods are taught by, for example, in Jager, K. F. et al., "Effect of Material Motion on Agglomeration in the Rotary Fluidized-Bed Granulator", Drugs Made in Germany, Vol. XXV, Pp. 61-65 (1982) which have been incorporated herein by reference. The term "total coat" refers to the proportion of coating to uncoated rotogranule in the coated rotogranule product, concentration of "polymer solution" to the proportion of polymer in the organic solvent solution, and "total batch" to the weight of medicament plus coating.

Example I

Rotogranulation/Coating of Famotidine.

Rotogranulation: Combine 5 kg of famotidine, 2 kg of PVP (Povidone grade K29/32-average molecular weight) and 33 kg of lactose impalpable in a rotogranulator bowl. Rotogranulate by spraying water (approximately 7 kg) at a rotor speed of 500 RPM. Dry the rotogranulated particles to a product temperature of 30-35° after decreasing the rotor speed to 250 RPM.

Particle Coating: Coat the particles produced in the rotogranulation step in a Wurster Coating apparatus. The polymer coating solution should consist of a 10% by weight solution of cellulose acetate 398-10 (39.8% acetyl content - 10 seconds viscosity) and PVP (Povidone K29/32-average molecular weight) where the ratio of CA to PVP is 80/20. The solvent used is an 80/20 mixture of acetone/methanol. Apply 10% by weight polymer to the particles. Maintain product temperature at about 41°C (106°F) during the coating step.

Example II

The procedure of Example I is carried out except that 1 kg of loperamide is substituted for 5 kg of famotidine and the amounts of lactose is increased to 37 kg.

Example III

The functions of several ingredients utilized in example III and some typical replacements for them are as follows:

Mannitol is a sweetener which can be replaced by dextrose, fructose, sorbitol, compressible sugar, and/or lactose;

Microcrystalline cellulose is used as a binder, and can be replaced with other binders such as alginic acid, carboxymethyl cellulose, hydroxypropylmethylcellulose, PVP, or starch;

Aspartame is an artificial sweetener which can be replaced with others such as saccharin;

Magnesium stearate is a lubricant (to lubricate the die walls and punches used during the tablet compression procedure). It can be replaced by talc, stearic acid, calcium stearate, zinc stearate, leucine, glycerides, sodium stearyl fumarate or the like; and

Artificial and natural flavor agents can be any conventional artificial and natural flavoring agents and flavor enhancers such as vanilla, grape, peppermint, orange, cherry, and/or spearmint flavors and conventional flavor enhancers or sweeteners.

PREPARATION OF CHEWABLE TABLETS

The ingredients displayed below were sieved, dry blended, and compressed by standard procedures into round (disc shaped) chewable tablets, each weighing 385 mg. Each tablet contained 10 mg. of active famotidine per tablet from coated rotogranules prepared in accordance with the procedure of Example 1 containing 10 weight percent CA:PVP; 80:20 coating.

EXAMPLE IV

Component	mg/Tablet
Famotidine, USP	10
Povidone USP (K29-32) (Granulation)	3.94
Lactose	64.95
Cellulose acetate	6.31
Povidone USP (coating)	1.58
Total of Coated Rotogranules	86.78

Ingredients and approximate weights	mg/Tablet	Per Batch, kg
Coated Particles	86.7	13.005
Mannitol USP, FL2080	259.2	38.88
Microcrystalline Cellulose (e.g. Avicel PH-101)	30	4.50
Aspartame	2.5	0.375
Prosweet Powder (Sugarless)	1.2	0.1845
Magnesium Stearate, NF	3.8	0.5775
Flavoring	1.5	0.2310
Coloring	0.4	0.06
Total Tablet Weight	385 mg	57.8 kg

The scope of the present invention is not limited by the description, examples and suggested used herein and modifications can be made without departing from the spirit of the invention. For example, other components may be added to the tablets including additional actives, various flavorings, preservatives and other pharmaceutical excipients. The present invention may also be used to provide a chewable form for vitamins, minerals or other nutrients.

Application of the compositions and processes of the present invention for medical and pharmaceutical uses can be accomplished by any clinical, medical and pharmaceutical methods and techniques as are presently and prospectively known to those skilled in the art. Thus it is intended that the present invention cover the modifications and variations of this invention provided that they come within the scope of the appended claims and their equivalents.

Claims

1. A chewable tablet of a medicament comprising compressed coated rotogranules, said coated granules individually comprising medicament which has been rotogranulated with a binder and a carrier material and coated with a polymer blend of cellulose acetate, cellulose acetate butyrate or a combination of both with polyvinylpyrrolidone.

2. The chewable tablet of claim 1, wherein the medicament is famotidine, loperamide, cimetidine, ranitidine, a salt thereof or a combination thereof.

3. The chewable tablet of claim 1 or claim 2, wherein the coating mixture has a weight ratio in the range of from 95:5 to 60:40 of cellulose acetate, cellulose acetate butyrate or a combination thereof to polyvinylpyrrolidone.

4. The chewable tablet of any one of claims 1 to 3, wherein the polymer blend coating comprises from 5 to 20% by weight of the total weight of the coated granules.

5. The chewable tablet of any one of claims 1 to 4, wherein the rotogranules comprise from 2 to 85% medicament, 4 to 10% binder and 10 to 94% carrier by weight of the total weight of the uncoated granule.

6. The chewable tablet of any one of claims 1 to 5, wherein the medicament is famotidine, the binder is polyvinylpyrrolidone and the carrier is lactose.

7. The chewable tablet of any one of claims 1 to 6, wherein the coated granules are substantially spherical in shape.

8. A rotogranulation composition for use in preparing a chewable tablet of any one of claims 1 to 7.

9. A process for producing coated medicament rotogranulations comprising the steps of:
preparing a rotogranulation composition of medicament, binder and a carrier; and
coating the medicament rotogranulation composition with cellulose acetate, cellulose acetate butyrate or a combination of both and polyvinylpyrrolidone.

10. The process of claim 9, further including the step of forming a chewable tablet by compressing the coated medicament rotogranulation composition in the presence of excipients.

11. The process of claim 9 or claim 10, which produces a product of any one of claims 1 to 8.

FIGURE 1

FIGURE 2

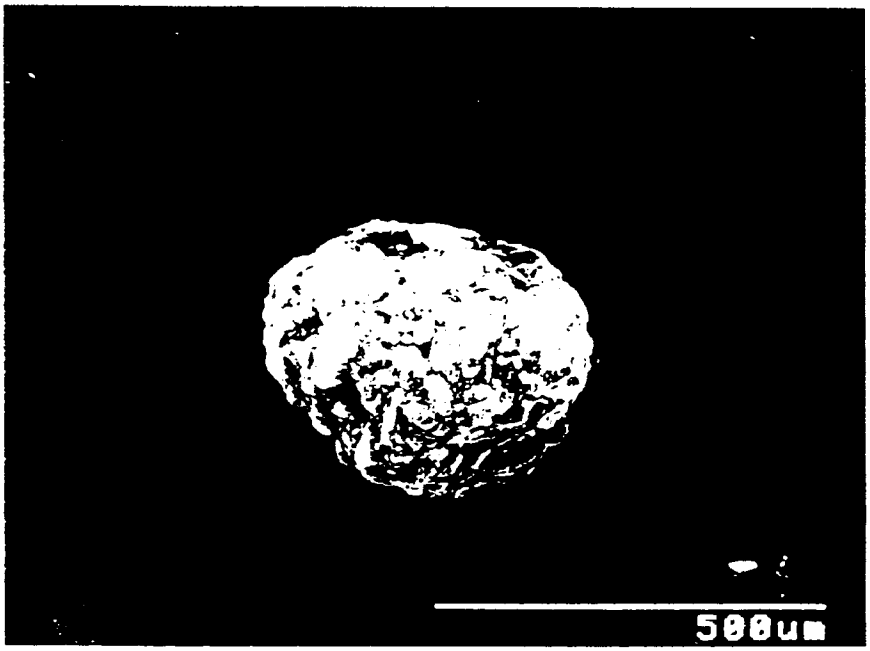
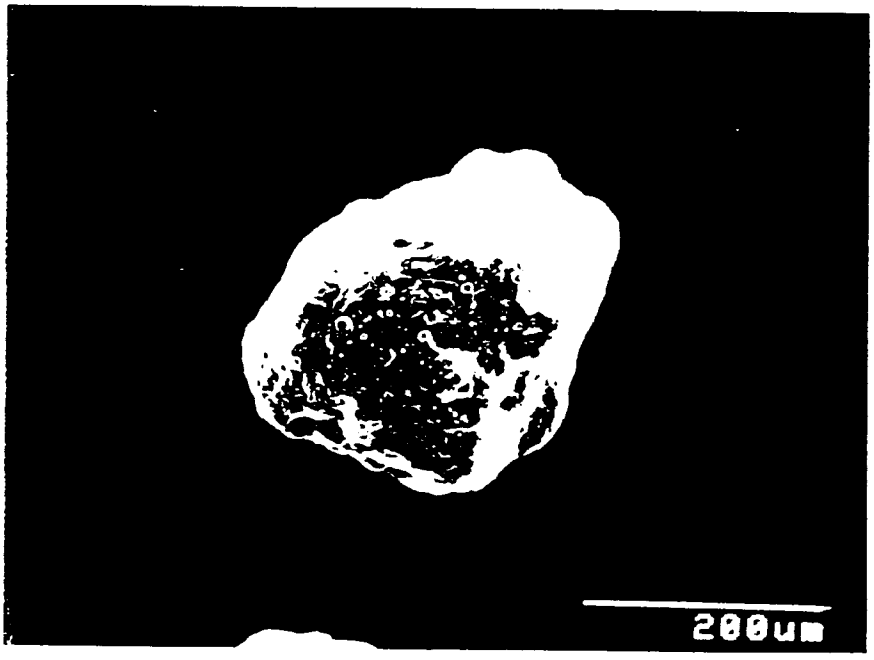


FIGURE 3



European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 30 7913

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y	EP-A-0 317 274 (MC NEIL CONSUMER PRODUCTS COMPANY) * page 2, line 42 - line 48 * * page 4, line 20 - line 56 * * page 10 - page 11; examples 12,13,15 * * claims *	1-5,7-11	A61K9/50 A61K9/52 A61K9/20
Y	GB-A-2 190 287 (BIREX RESEARCH AND DEVELOPMENT LTD AND CARMILTON LTD) * page 1, line 38 - line 63 * * page 2; example 1 *	1-5,7-11	
A	WO-A-8 908 448 (HOLMES M.J. AND NYCOMED AS) * page 1, line 1 - line 2 * * page 2, paragraph 3 * * page 4, paragraph 4 * * page 6; example 1 * * claims 1,11 *	1-11	
A	EP-A-0 349 103 (SMITH KLINE & FRENCH LABORATORIES LTD) * page 2, line 1 - line 3 * * page 3, line 55 * * page 4, line 1 - line 16 * * page 5; example 1 *	1-11	TECHNICAL FIELDS SEARCHED (Int. Cl.5) A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	19 NOVEMBER 1991	BOULOIS D.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)